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# Bone texture analysis is correlated with three-dimensional microarchitecture and mechanical properties of trabecular bone in osteoporotic femurs

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**Abstract** Fracture of the proximal femur is a major public health problem in elderly persons. It has recently been suggested that combining texture analysis and bone mineral density measurement improves the failure load prediction in human femurs. In this study, we aimed to compare bone texture analysis with three-dimensional (3D) microarchitecture and mechanical properties of trabecular bone in osteoporotic femurs. Eight femoral heads from osteoporotic patients who fractured their femoral neck provided 31 bone cores. Bone samples were studied using a new high-resolution digital X-ray device (BMA<sup>TM</sup>, D3A Medical Systems) allowing for texture analysis with fractal parameter  $H_{\text{mean}}$ , and were examined using micro-computed tomography (microCT) for 3D microarchitecture. Finally, uniaxial compression tests to failure were performed to estimate failure load and apparent modulus of bone samples. The fractal parameter  $H_{\text{mean}}$  was strongly correlated with bone volume fraction (BV/TV) ( $r = 0.84$ ) and trabecular thickness (Tb.Th) ( $r = 0.91$ ) ( $p < 0.01$ ).  $H_{\text{mean}}$  was also markedly correlated with failure load ( $r = 0.84$ ) and

apparent modulus ( $r = 0.71$ ) of core samples ( $p < 0.01$ ). Bone volume fraction (BV/TV) and trabecular thickness (Tb.Th) demonstrated significant correlations with failure load ( $r = 0.85$  and  $0.72$ , respectively) and apparent modulus ( $r = 0.72$  and  $0.64$ , respectively) ( $p < 0.01$ ). Overall, the best predictors of failure load were  $H_{\text{mean}}$ , bone volume fraction, and trabecular thickness, with  $r^2$  coefficients of  $0.83$ ,  $0.76$ , and  $0.80$  respectively. This study shows that the fractal parameter  $H_{\text{mean}}$  is correlated with 3D microCT parameters and mechanical properties of femoral head bone samples, which suggests that radiographic texture analysis is a suitable approach for trabecular bone microarchitecture assessment in osteoporotic femurs.

**Keywords** Osteoporosis · Femur · Fracture · Trabecular bone · Texture analysis

## Introduction

Fracture of the proximal femur is a major public health problem in elderly persons, representing the main source of osteoporosis-related mortality and morbidity [1]. Bone strength is routinely estimated using bone mineral density (BMD), as measured by dual-energy X-ray absorptiometry (DXA) [2, 3]. The current definition of osteoporosis is a BMD T-score that is more than 2.5 standard deviations (SD) below the peak bone mass [4]. Each 1-SD decrease in BMD is associated with a 1.5- to 3.0-fold increase in osteoporotic fracture risk [4]. However, many individuals without densitometric osteoporosis are at increased risk of fracture; and up to 50 % of fractures occur among individuals who would not be classified as osteoporotic based on DXA measurement [5–7]. Hence, bone strength depends not only on the amount of bone tissue, but also on its spatial distribution, cortical and trabecular microarchitecture, bone turnover, and material

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properties such as matrix mineralization, collagen polymorphisms, and microdamage [8]. Thus, in 2000, the National Institute of Health defined in addition to a decreased bone mass new “quality” criteria for the diagnosis of osteoporosis. As these quality criteria are not evaluated by DXA, alternative imaging techniques have been developed to assess bone microarchitecture and improve fracture risk prediction [9–14].

Microarchitecture deterioration can be assessed in vivo using high-resolution quantitative computed tomography (QCT) and magnetic resonance imaging (MRI). Nevertheless, for obvious cost and availability reasons, these modalities are not routinely accessible in the study of large populations. On the other hand, digital radiography is a widely available imaging modality that, with a spatial resolution of up to 40  $\mu\text{m}$ , has the potential to reflect bone microarchitecture [13]. As trabecular and cortical bone are superimposed, only a texture of trabecular bone is resolved rather than its actual three-dimensional (3D) architecture [14]. Despite this technical limitation, radiographic texture analysis can characterize trabecular bone microarchitecture via two-dimensional (2D) projection images (gray-level projection) and calculation of the fractal parameter  $H_{\text{mean}}$ . Previous studies have suggested that fractal analysis of bone texture is correlated with 3D microarchitecture parameters and is independent of BMD for determining the fracture risk [15–19]. Recently, a new high-resolution X-ray device with direct digitization, named BMA<sup>TM</sup>, has been developed to provide a better precision of texture parameters than previously obtained on digitized films [20–22]. However, although two studies conducted on cadaveric femurs have demonstrated correlations between 2D textural analysis on radiographic images and 3D microCT parameters, very few data support the qualitative similarity of radiographic texture analysis to 3D microCT parameters in osteoporotic patients [23, 24].

In this work, we studied femoral head bone samples from patients who fractured their femoral neck, using this high-resolution X-ray device to estimate the fractal parameter  $H_{\text{mean}}$ . Our primary objectives were to compare bone texture features with 3D structural parameters and mechanical properties of trabecular bone, and to determine if radiographic texture analysis can be considered an alternative method to microCT for evaluating bone microarchitecture in osteoporotic femurs.

## Materials and methods

### Patient selection

In compliance with institutional safety and ethics regulations, human femoral heads were obtained from 8 female

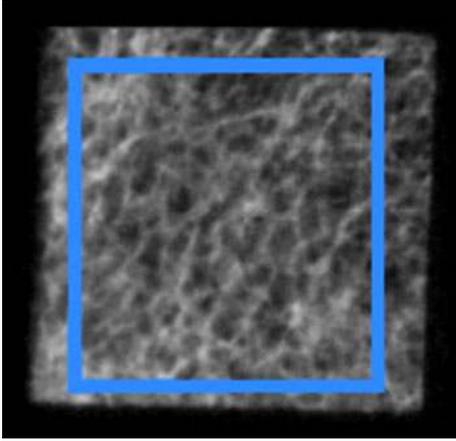
donors (average age 84 years, range 72–97) who underwent hip arthroplasty for osteoporotic femoral neck fracture. All patients gave informed consent. Osteoporotic fracture was defined as a fracture without preceding trauma or in response to minimal trauma. Patients suffering from hip fractures after severe traumas as well as patients with known diseases that could interfere with bone metabolism (such as osteomalacia, bone cancer, myeloma, Paget’s disease, rheumatoid arthritis, hyperparathyroidism, hyperthyroidism, severe renal or hepatic insufficiency), and patients treated with corticosteroids, fluoride, bisphosphonates, and calcitonin in the last year before inclusion were excluded from this study. Specimens were stored at  $-20\text{ }^{\circ}\text{C}$  prior to and in between the tests.

### Sample preparation

A total of 31 cubic bone cores measuring 10 mm in length were obtained from the 8 frozen specimens along the longitudinal axis of the femoral head. Two additional bone cores were not usable and thus excluded. Bone marrow was extracted by a succession of baths in water at  $37\text{ }^{\circ}\text{C}$ , followed by an extraction with an air jet. This procedure ensured a total fluid removal without altering the trabecular structure.

### Bone texture analysis

A high-resolution X-ray device (BMA<sup>TM</sup>, D3A Medical Systems, Orleans, France) with a new  $15 \times 23\text{-cm}$  detector with a  $50\text{-}\mu\text{m}$  pixel size was used to obtain digitized anterior–posterior radiographs of these bone samples. The following parameters were used: 40 kV, 10 mA, and 0.8 m focal distance. During the study, a calibration test was carried out each day of examination using an external phantom to detect any potential drift of the instrumentation [20]. A single square region of interest (ROI) of 280 pixels was positioned at the center of the bone core (Fig. 1). Every sample was scanned twice with repositioning to assess the precision of the measurement. The texture parameters obtained were the fractal dimension  $H_{\text{mean}}$ , co-occurrence matrix, and run-length matrix [21]. The gray levels of the ROIs were fitted to the most used fractal model for texture images: the fractional Brownian motion. Fractal shapes were then described by a single parameter,  $H$  (Hurst exponent), related to the fractal dimension,  $D$ , by  $H = 2 - D$  [21]. For gray-level run-length analysis, adjacent pixel runs ( $n, n + 1$ ) were defined in a given direction and parameters were computed based on the run-length distribution histogram [22]. Co-occurrence matrices characterized the joint probability of having a pair of gray levels separated by a given distance in a given direction [22].



**Fig. 1** Microradiographic image showing the ROI (blue square) positioning for bone texture analysis in a core sample (color figure online)

### Microcomputed tomography

High resolution microCT tomography (Skyscan<sup>®</sup> 1172, Kontich, Belgium) was used to image trabecular bone at an isotropic voxel size of 20  $\mu\text{m}$ . This system operates in the cone-beam method and comprises a sealed microfocus X-ray tube with a spot size less than 8  $\mu\text{m}$  and an 11 Mp 12-bit CCD camera. Projection images were obtained at 80 kV and 100  $\mu\text{A}$  with a 0.5 mm aluminium filter. The following parameters were determined using the Skyscan CT-analyser software: (1) bone volume fraction (BV/TV, in %), the ratio of 3D total bone volume to the total core volume); (2) average trabecular thickness (Tb.Th, in mm); (3) trabecular number (Tb.N, the inverse of the mean distance between the mid-axes of the structures, per millimeter); and (4) trabecular separation (Tb.Sp, the mean distance of the non-bone regions, in mm).

### Mechanical testing

Following all imaging steps, the core samples underwent mechanical testing at room temperature using a universal testing machine (Instron 5566, Instron, Canton, MA, USA). A uniaxial compressive load was applied at a displacement rate of 10 mm/min with a maximum compressive strain of 60 %, in the same loading direction. Samples were placed between 2 polished dense steel platens. In order to reduce the effect of friction, the steel platens were initially lubricated with saline solution. Failure load (in N) was defined as the first local maximum where the load subsequently declined more than 10 %.

### Statistical analysis

Statistical analyses were performed with SPSS (SPSS, Chicago, IL, USA). Descriptive statistics (mean and SD)

were computed for all study parameters. No significant differences from normal distributions were found. For the reliability analysis, the intraclass correlation coefficient (ICC) with 95 % confidence interval and coefficient of variation (CV) were used. For univariate analysis, we used the Spearman coefficient to assess correlations between, respectively, bone texture, 3D structure, and mechanical parameters. To identify the best predictors of failure load, multiple regression models were computed from the set of independent variables that were significantly correlated with failure load in the univariate analysis. Multiple regression models were compared using the extra sum-of-squares  $F$  test.

The minimum probability level for accepting significance ( $p$ ) was set at 0.05.

### Results

The descriptive statistics for bone texture and 3D structure parameters, and correlations with mechanical properties are reported in Table 1. The fractal parameter  $H_{\text{mean}}$  demonstrated significant correlations with failure load ( $r = 0.84$ ) and apparent modulus ( $r = 0.71$ ) of core samples ( $p < 0.01$ ) (Fig. 2). In the same way, bone volume fraction (BV/TV) and trabecular thickness (Tb.Th) were markedly correlated with failure load ( $r = 0.85$  and  $0.72$ , respectively) and apparent modulus ( $r = 0.72$  and  $0.64$ , respectively) ( $p < 0.01$ ).

Reproducibility (ICC with 95 % confidence interval and CV) of textural parameters measurements with repositioning of the specimens is shown in Table 2.

Univariate analysis demonstrated that  $H_{\text{mean}}$  was significantly correlated with bone volume fraction (BV/TV) ( $r = 0.84$ ) and trabecular thickness (Tb.Th) ( $r = 0.91$ ,  $p < 0.01$ ) (Table 3; Fig. 3). In addition, co-occurrence and run-length matrices demonstrated significant correlations with the bone volume fraction ( $p < 0.05$ ).

The results of multiple regression analysis are shown in Table 4.  $H_{\text{mean}}$ , bone volume fraction, and average trabecular thickness were the best predictors of failure load with  $r^2$  coefficients of 0.83, 0.76, and 0.80, respectively. The  $F$  statistic demonstrated no significant difference in terms of failure load prediction between  $H_{\text{mean}}$  and the two previously mentioned microCT parameters.

### Discussion

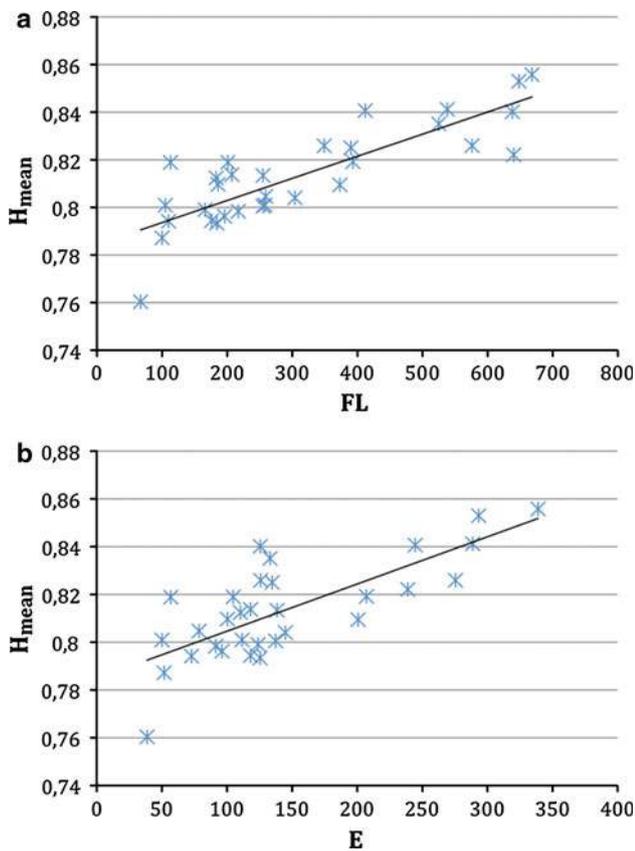
Osteoporotic hip fractures are associated with an increased mortality and a reduced quality of life [1]. The standard diagnostic technique for assessing osteoporosis and monitoring therapy is DXA measuring BMD [2, 3]. However,

**Table 1** Mean and SD for each imaging variable and correlation with failure load ( $FL$ ) and apparent modulus ( $E$ )

	Mean $\pm$ SD	FL ( $r$ )	$E$ ( $r$ )
$H_{\text{mean}}$	0.813 $\pm$ 0.020	0.84**	0.71**
Co-occurrence	2.116 $\pm$ 0.034	0.215	0.092
Run-length	1.816 $\pm$ 0.032	0.168	0.066
BV/TV	23.860 $\pm$ 6.120	0.85**	0.72**
Tb.Th	0.248 $\pm$ 0.059	0.72**	0.64**
TbN	0.971 $\pm$ 0.186	0.19	0.17
TbSp	0.781 $\pm$ 0.110	-0.11	-0.21

BV/TV bone volume fraction, Tb.Th average trabecular thickness, TbN trabecular number, TbSp trabecular separation, SD standard deviation

\*\*  $p < 0.01$



**Fig. 2** Graph displaying the relation observed between  $H_{\text{mean}}$  (ordinate) and failure load (in N, abscissa) (a), and between  $H_{\text{mean}}$  (ordinate) and apparent modulus E (in MPa, abscissa) (b)

although BMD can predict femoral bone strength to some extent, other determinants of the so-called bone quality contribute to bone strength, such as macroarchitecture, microarchitecture, mineralization, size and quality of the crystal, distribution and quality of collagen cross-links, and rate of bone turnover [25, 26]. Microarchitecture is in particular one of the most relevant contributors to bone

**Table 2** Reproducibility of textural parameters (measured twice with repositioning of the specimen) using ICC with 95 % confidence interval and CV

	ICC	CV (%)
$H_{\text{mean}}$	0.82 (0.61; 0.95)	2.1
Co-occurrence	0.84 (0.67; 0.94)	1.8
Run-length	0.80 (0.62; 0.91)	1.9

strength and is part of the definition of osteoporosis [27]. As osteoporosis decreases the thickness and number of trabeculae and increases trabecular separation, it alters X-ray attenuation in bone and thereby changes the density and texture of the image [28]. The issue of whether bone texture analysis has the potential to assess some bone quality aspects complementary to and independent from BMD measurements has thus become a crucial research topic. Previous studies have demonstrated that the texture of projectional images obtained by radiography reflects trabecular bone microarchitecture and exhibits the properties of fractals [17–19]. The alterations of trabecular bone provide an increase in fractal dimension, which means a decrease of the  $H_{\text{mean}}$  parameter [29]. Generally, this decrease of the fractal parameter  $H_{\text{mean}}$  is considered to be an index of higher image irregularity or complexity. So, the less isotropic the bone texture is, the lower the mechanical properties are [30, 31]. The potential interest in texture analysis has been highlighted in clinical studies, suggesting that DXA and texture analysis assess different bone parameters [21, 32]. All these data suggest that texture information contained in trabecular bone structure may determine local bone quality independently from BMD [29, 31].

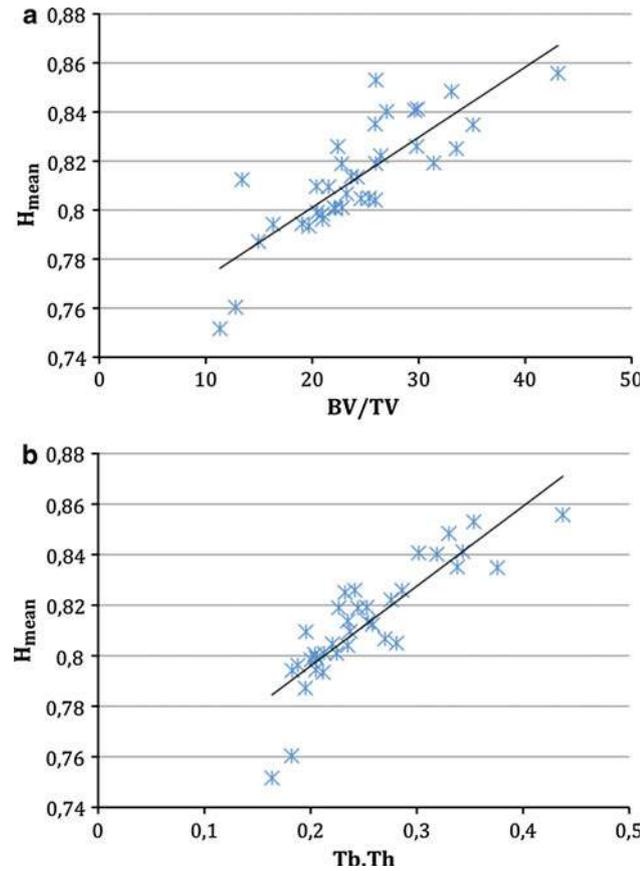
To refine bone strength prediction, we studied the femoral heads from osteoporotic patients to compare the radiographic texture features with the 3D structural parameters and mechanical properties of trabecular bone. As accurate site-matched analysis of 3D bone microarchitecture and texture analysis can be difficult to perform, we chose to perform radiographic texture analysis on bone cores instead of entire bone specimens to obtain a more meaningful correlation between bone texture and microCT parameters. We used a high-resolution digital X-ray device to obtain a better precision of textural parameters than that of secondary digitization of radiographic images [20]. As one of the main challenges in bone texture analysis is the choice of appropriate and reproducible ROIs, in our study the ROI was positioned in a standardized fashion allowing a high reproducibility between two independent acquisitions [24, 25, 33]. This could be related to the larger proportion of trabecular bone contained in the femoral head, which generates well-textured images with better

**Table 3** Correlation coefficients between textural and 3D structure parameters

	$H_{\text{mean}}$	Co-occurrence	Run-length
BV/TV	0.84**	0.50*	-0.48*
Tb.Th	0.91**	0.34	-0.26
TbN	0.01	0.29	-0.33
TbSp	0.06	-0.24	0.28

BV/TV bone volume fraction, Tb.Th average trabecular thickness, TbN trabecular number, TbSp trabecular separation

\*  $p < 0.05$ , \*\*  $p < 0.01$



**Fig. 3** Graph displaying the relation observed between  $H_{\text{mean}}$  (ordinate) and bone volume fraction (in %, abscissa) (a), and between  $H_{\text{mean}}$  (ordinate) and trabecular thickness (in  $\mu\text{m}$ , abscissa) (b)

reproducibility coefficients. Interestingly, our data also show that, although the fractal parameter  $H_{\text{mean}}$  was obtained using a model based on the fractional Brownian motion, and co-occurrence and run-length matrices are statistical methods describing the differential characteristics of local gray level, the three textural parameters were each significantly correlated with 3D structure parameters in our study ( $p < 0.05$ ). In addition, as bone texture parameters obtained by fractal analysis reflect mechanical

**Table 4** Multiple regression analysis of imaging parameters used to explain the failure load

	$r^2$
$H_{\text{mean}}$	0.83
BV/TV	0.76
Tb.Th	0.80

The significance level required to enter the equation is  $p < 0.05$

BV/TV bone volume fraction, Tb.Th average trabecular thickness

properties, the fractal parameter  $H_{\text{mean}}$  was significantly correlated with bone strength in our study ( $p < 0.01$ ). Our microarchitecture and biomechanical correlation studies are thus in accordance: fractal dimension increases when trabecular thickness decreases, or when bone strength decreases [16, 23]. The increase of  $H_{\text{mean}}$  reflects a higher complexity of the image, likely related in osteoporotic femurs to changes of the trabecular network: focal perforation of trabecular plates, disconnection and disappearance of some trabeculae [16, 23]. Surprisingly, our study did not show a significant correlation between the fractal parameter  $H_{\text{mean}}$  and trabecular number or trabecular separation. This lack of correlation may be related to the age of our population (mean age 84 years, all cases over 70), which limits the range of variation of connectivity indices and of  $H_{\text{mean}}$ , and also to the limited sample size of cancellous bone. Nevertheless, when compared to histomorphometric indices measured on calcaneus biopsies, the fractal parameter  $H_{\text{mean}}$  is correlated with trabecular separation and trabecular number, suggesting that  $H_{\text{mean}}$  reflects more bone microarchitecture than bone mass [16]. Besides, our study did not involve anisotropy evaluation, as a previous work specifically addressed this consideration using the same approach in the calcaneus [19]. Finally, in our cohort, multiple regression analysis demonstrated that the fractal parameter  $H_{\text{mean}}$  provides a similar performance in failure load prediction to that of 3D microCT parameters. In whole femur, cortical bone properties (density, thickness, composition) together with bone geometry and trabecular properties (architecture, density, composition) are all significant contributors to bone strength. Our study assessed only the trabecular properties, independent of their roles in the contribution to whole bone strength. The significance of structural measurements in whole bone, where trabecular architecture may be analyzed in larger areas, still needs to be evaluated in the context of their relationships with cortical bone properties and whole bone geometry [22, 23].

Although bone texture analysis is not a technique directly assessing 3D architecture, this tool for characterizing bone microarchitecture could be applied clinically to radiographs to detect bone changes related to age and

osteoporosis leading to bone strength decrease. Bone loss in osteoporosis occurs uniformly throughout the femoral head, leading to an overall decrease in bone mass, and to lower bone volume fraction and trabecular thickness [34]. BMD is largely related to bone volume fraction whereas textural features are a more complex mixture of 3D structure parameters.

Some limitations may be considered inherent in the materials and methods used in this study. Although the use of frozen human specimens allowed us to draw a conclusion about actual bone strength, we acknowledge that using these types of specimens limits application in vivo. First, our group of specimens was relatively small, with a history of osteoporotic fracture of the femoral neck, and therefore cannot be considered a normal population in regards to bone status. Second, since the results of this study are based on the evaluation of bone core specimens, their generalization to the analysis of entire bones ex vivo or in vivo is limited. In particular, further experimentation is necessary to assess the role of bone marrow, cortical bone, and soft tissue. Here note that inclusion of cortical bone may generate a parasitic texture on the projection image. In the same way, in vivo, the increase in X-ray scatter and blurring due to the overlying soft tissues may adversely affect the performance of a computerized system, since textural parameters are related to the blurring effect. Third, trabecular bone analysis was limited in our study to the femoral head only. Here note that, although most of the age-related changes in trabecular structure occur in the femoral neck, altered microarchitecture and increased anisotropy have also been described in the center of osteoporotic femoral heads [35]. Finally, it is important to recognize that 2D texture parameters do not provide true quantitative measurements of the physical bone structure, but rather an indirect assessment using a model based on the fractional Brownian motion. The correlation of radiographic texture analysis to 3D microCT parameters that we have established in our study may allow rational 2D parameter selection based on the understanding of the mechanical behavior of 3D structural properties [23]. Thus, the methods detailed in the present study could provide an evaluation of bone structure in vivo that conventional BMD measurement cannot offer.

In summary, the major findings in our study were that (1) bone texture parameters that intuitively appear to be similar to established 3D structure parameters were correlated with actual 3D microCT measurements, and that (2) 2D and 3D trabecular measurements were individually correlated with bone strength of the femoral cores. To the best of our knowledge, this study is the first to suggest that radiographic texture analysis is a suitable approach to trabecular bone microarchitecture assessment in osteoporotic femurs ex vivo. As application of texture analysis at the

proximal femur is known to be challenging in the clinical situation, given the potential positioning problems and amount of overlying soft tissue, further studies in osteoporotic patients are needed to evaluate correlations of bone texture parameters measured in vivo to 3D microCT and bone strength measured ex vivo.

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**Conflict of interest** The authors have no conflict of interest.

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